Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing.

Bibliographic Source(s)

Relling MV, Gardner EE, Sandborn WJ, Schmiegelow K, Pui C-H, Yee SW, Stein CM, Carrillo M, Evans WE, Klein TE, Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. Clin Pharmacol Ther. 2011 Mar;89(3):387-91. [33 references] PubMed

Guideline Status

This is the current release of the guideline.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) reaffirmed the currency of the guideline in 2013.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Interpretation of Genetic Tests

Table 1 below summarizes the assignment of the likely thiopurine methyltransferase (TPMT) phenotype on the basis of the most common * allele diplotypes, and these assignments are used to link genotypes with thiopurine dosing. Although inactivating *TPMT* alleles have been extensively studied in several populations (see Supplementary Tables S3 and S4 in the "Availability of Companion Documents" field), one of the limitations inherent in a commercial genotype-only test is that rare or previously undiscovered variants will generally not be detected.

Table 1. Assignment of Likely Thiopurine Methyltransferase Phenotypes Based on Genotypes

Likely Phenotype	Genotypes	Examples of Diplotypes
Homozygous wild-type or normal, high activity (constitutes ~86–97%[a] of patients)	An individual carrying two or more functional (*1) alleles	*1/*1
Heterozygote or intermediate activity (~3–14%[a] of patients)	An individual carrying one functional allele (*1) plus one nonfunctional allele (*2, *3A, *3B, *3C, or *4)	*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4

Likely Phenotype	Genotypes	Examples of Diplotypes
Homozygous variant, mutant, low, or deficient activity (~1 in 178 to 1 in 3,736 patients[a])	An individual carrying two nonfunctional alleles (*2, *3A, *3B, *3C, or *4)	*3A/*3A, *2/*3A, *3C/*3A, *3C/*4, *3C/*2, *3A/*4

[a]See Supplementary Data (in the "Availability of Companion Documents" field) for estimates of phenotype frequencies among different ethnic/geographic groups.

Dosage Recommendations

Thiopurines are most commonly used to treat nonmalignant conditions but are also critical anticancer agents. The approach to dosing adjustments based on TPMT status may differ depending on the clinical indication and the propensity to initiate therapy at higher vs. lower starting doses. The guideline authors and others advocate testing for TPMT status prior to initiating thiopurine therapy, so that starting dosages can be adjusted accordingly.

Thiopurines are used as immunosuppressants in inflammatory bowel disease, rheumatoid arthritis, and other immune conditions. In most of these diseases, the selection of medications is carried out stepwise, with multiple nonthiopurine (and nonmyelosuppressive) agents being available as alternatives. Several consensus guidelines for treatment of nonmalignant diseases explicitly recommend preemptive TPMT testing coupled with customized starting doses of thiopurines. A survey calling for responses from pediatric gastroenterologists revealed that 61% of child patients were tested for TPMT before starting thiopurine therapy, and the average rates of preemptive testing reported by non-cancer specialists in the United Kingdom were 47%–94%.

In nonmalignant conditions, if one starts with low doses in all patients in order to avoid severe toxicity in the minority with a *TPMT* defect, one risks disease progression during the period of upward dosage titration. In nonmalignant conditions, full starting doses are recommended for homozygous wild-type carriers, reduced doses (30%–70% of target dose) in those who are heterozygous for *TPMT*, and substantially reduced doses (or use of an alternative agent) in the rare homozygous deficient patients (see Table 2 below).

Thiopurines have a unique role in the treatment of several malignancies. Conventional starting doses of thiopurines are generally "high" because these doses have been derived from trials heavily weighted by the ~86%–97% of the population who are wild-type for *TPMT* and receive maximal tolerable doses by the standards of anticancer treatment (hence, full doses should be given to those who are homozygous wild-type for *TPMT*; see table below). Given that starting doses have tended to be high (e.g., 75 mg/m^2 of mercaptopurine [MP]) in cancer (e.g., in acute lymphoblastic leukemia), lower-than-normal starting doses should be used in heterozygous deficient patients and markedly reduced doses (at least 10-fold reduction) in homozygous deficient patients (see Table 2, below). This approach has decreased the risk of acute toxicity without compromising relapse rates in acute lymphoblastic leukemia. Even at these markedly reduced dosages, erythrocyte thioguanine nucleotide (TGN) concentrations in homozygous deficient patients remain well above those tolerated and achieved by the majority of patients (who are wild-type for *TPMT*).

There are varying practices about when—and even whether—to test for TPMT status in oncology patients who receive thiopurines. Because of the rarity of malignancies and defective *TPMT* genotypes, no randomized clinical trials have proven the benefit of customizing starting doses of thiopurine based on TPMT status in cancer settings. Nevertheless, many cancer clinicians preemptively test TPMT status to customize starting doses of thiopurines, basing their decision on the strong mechanistic data and retrospective analyses of clinical trials supporting a lower dose in those with a TPMT defect (see Supplementary Table S5 online and in the "Availability of Companion Documents" field). Thiopurines are almost always used as part of combination chemotherapy that contains multiple myelosuppressive medications. Therefore, a trial-and-error approach (i.e., starting thiopurine therapy without ascertaining the TPMT status) has some disadvantages. The duration of myelosuppression varies substantially—an extremely long period of myelosuppression can result if conventional thiopurine doses are given to a patient with low TPMT activity, thereby delaying ongoing chemotherapy. Also, it is impossible to determine, through clinical monitoring alone, which of several myelosuppressive agents is the most likely cause of myelosuppression. Another reason to test every patient preemptively is that even a short full-dose course of thiopurines can result in death or severe myelosuppression in the rare homozygous deficient individual. Such an eventuality could be avoided by preemptive testing and starting with dramatically decreased doses (more than 10-fold lower than normal doses) of thiopurine or choosing an alternative therapy for the potentially at-risk patients.

Some of the clinical data on which dosing recommendations are based (see Table 2 below) rely on measures of TPMT phenotype rather than genotype; however, because *TPMT* genotype is so strongly linked to TPMT phenotype, these recommendations should apply regardless of the method used to assess TPMT status.

Table 2. Recommended Dosing of Thiopurines by Thiopurine Methyltransferase Phenotype

	MP	Azathioprine	TG

Phenotype	Implications for MP and Azathioprine Pharmacologic Measures	Dosing Recommendations for MP	Classification of Recommendations	Dosing Recommendations for Azathioprine	Classification of Recommendations	Implications for Pharmacologic Measures after TG	Dosing Recommendations for TG	Classification of Recommendations
Homozygous wild-type or normal, high activity	Lower concentrations of TGN metabolites, higher methylTIMP, this is the "normal" pattern	Start with normal starting dose (e.g., 75 mg/m^2/d or 1.5 mg/kg/d) and adjust doses of MP (and of any other myelosuppressive therapy) without any special emphasis on MP compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment (Weinshilboum, 2003; Colletti et al., 2009; Evans et al., 1991).	Strong	Start with normal starting dose (e.g., 2–3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment (Weinshilboum, 2003; Meggitt, Gray, & Reynolds, 2006; Evans et al., 1991).	Strong	Lower concentrations of TGN metabolites, but note that TGN after TG are 5–10× higher than TGN after MP or azathioprine	Start with normal starting dose. Adjust doses of TG and of other myelosuppressive therapy without any special emphasis on TG. Allow 2 weeks to reach steady state after each dose adjustment (Weinshilboum, 2003; Lennard & Lilleyman, 1996).	Strong
Heterozygote or intermediate activity	Moderate to high concentrations of TGN metabolites; low concentrations of methylTIMP	Start with reduced doses (start at 30%–70% of full dose: e.g., at 50 mg/m^2/d or 0.75 mg/kg/d) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In those who require a dosage reduction based on myelosuppression, the median dose may be ~40% lower (44 mg/m^2) than that tolerated in wild-type patients (75 mg/m^2) (Black et al., 1998; Nygaard, Toft, & Schmiegelow, 2004). In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing MP over other agents (Weinshilboum, 2003; Evan et al., 2001; Higgs et al., 2010; Aricó et al., 2005; Relling et al., 2010; Colletti et al., 2009; Evans et al., 1991; Lennard, 1998; Krynetski & Evans, 1998).	Strong	If disease treatment normally starts at the "full dose," consider starting at 30%–70% of target dose (e.g., 1–1.5 mg/kg/d), and titrate based on tolerance. Allow 2–4 weeks to reach steady state after each dose adjustment (Weinshilboum, 2003; Meggitt, Gray, & Reynolds, 2006; Evans et al., 1991; Lennard, 1998).	Strong	Moderate to high concentrations of TGN metabolites; but note that TGN after TG are 5–10× higher than TGN after MP or azathioprine	Start with reduced doses (reduce by 30%–50%) and adjust doses of TG based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing TG over other agents (Weinshilboum, 2003; Lennard & Lilleyman, 1996).	Moderate
Homozygous variant, mutant, low, or deficient activity	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no methylTIMP metabolites	For malignancy, start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to thrice weekly instead of daily, e.g., 10 mg/m^2/d given just 3 days/week) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing MP over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy (Weinshilboum, 2003; Anstey, Wakelin, & Reynolds, 2004; Evans et al., 1991; Lennard, 1998).	Strong	Consider alternative agents. If using azathioprine start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. Azathioprine is the likely cause of myelosuppression (Meggitt, Gray, & Reynolds, 2006; Evans et al., 1991; Relling et al., 2006; Lennard, 1998; Kaskas et al., 2003).	Strong	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease	Start with drastically reduced doses (Lennard & Lilleyman, 1996) (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of TG based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing TG over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy (Weinshilboum, 2003).	Strong

MP, mercaptopurine; TG, thioguanine; TGN, thioguanine nucleotide; TIMP, secondary metabolite of MP.

Definitions:

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Conditions requiring thiopurine therapy, including:

- Nonmalignant immunologic disorders (e.g., inflammatory bowel disease, rheumatoid arthritis)
- Lymphoid malignancies
- Myeloid leukemias

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Allergy and Immunology

Family Practice

Gastroenterology

Internal Medicine

Medical Genetics

Oncology

Pediatrics

Pharmacology

Preventive Medicine

Rheumatology

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide information with which to interpret clinical thiopurine methyltransferase (*TPMT*) genotype tests so that the results can be used successfully to guide the dosing of thiopurines

Target Population

Adults and children with conditions requiring thiopurine therapy

Interventions and Practices Considered

Thiopurine therapy (azathioprine, mercaptopurine, thioguanine) based on thiopurine methyltransferase (*TPMT*) genotype tests

Major Outcomes Considered

- Risk for myelosuppression with thiopurine therapy
- Tolerance of thiopurine therapy
- Risk for toxicity with thiopurine therapy
- Adverse effects of thiopurine therapy
- Therapeutic effects of thiopurine therapy

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The guideline authors searched the PubMed database (1966 to May 2010 and Ovid MEDLINE (1950 to May 2010) for keywords ((TPMT) OR (thiopurine methyltransferase) OR thiopurine S-methyltransferase) AND (thiopurine OR mercaptopurine OR thioguanine OR azathioprine) for the contribution thiopurine methyltransferase (*TPMT*) genotype had on predicting a thiopurine-related adverse drug event (ADE) or outcome. Definitive reviews were relied upon to summarize much of the earlier literature.

To construct a *TPMT* minor allele frequency table (see Supplemental Table S3 in the "Availability of Companion Documents" field) based on ethnicity, the following search criteria were used: (TPMT) OR (thiopurine) AND ((allele) OR (frequency) OR (genotype)). Studies were considered for inclusion if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or minor allele percentages for *TPMT* genotypes were reported, (3) the method by which *TPMT* was genotyped was reliable and proven (no proof-of-principle experiments), (4) the sample population consisted of at least 50 patients, and (5) the study represented an original publication (no reviews). The combined analysis included 8,676 Caucasians, 2,938 Mediterraneans, 1,028 South Americans, 1,146 Africans, 8,377 Asians, 600 South West Asians, 507 Mexicans, and 2,403 Middle Easterners. A similar search strategy was used to gather the body of evidence related to the use of thiopurines in specific disease states and the relative contribution *TPMT* genotype had on predicting a thiopurine-related adverse drug event (ADE).

2013 Reaffirmation

The guideline authors searched the PubMed database (1966 to October 2012) and Ovid MEDLINE (1950 to October 2012) for keywords ([TPMT] OR [thiopurine methyltransferase] OR thiopurine S-methyltransferase) AND (thiopurine OR mercaptopurine OR thioguanine OR azathioprine) for the contribution thiopurine methyltransferase (*TPMT*) genotype had on predicting a thiopurine-related adverse drug event or outcome. Definitive reviews were relied upon to summarize much of the earlier literature.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Clinical Pharmacogenetics Implementation Consortium's dosing recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data (see Table S5 in the online Supplemental material; see the "Availability of Companion Documents" field), as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting dosage recommendations include: *in vivo* clinical outcome data for thiopurines, *in vivo* pharmacokinetic and pharmacodynamic data for thiopurines, *in vitro* enzyme activity of expressed wild-type or variant-containing thiopurine methyltransferase (TPMT) (with thiopurines as substrate), *in vitro* TPMT enzyme activity from tissues isolated from individuals of known *TPMT* genotypes, *in vivo* pre-clinical pharmacokinetic and pharmacodynamic studies, and *in vitro* studies of TPMT protein stability or enzyme activity.

2013 Reaffirmation

Although the guideline authors are not modifying the original main guideline, they have updated the Supplementary Data online to include additional studies that further support the original recommendations (see Supplementary Table S5 online and the Other Considerations subsection of the Supplementary Data online in the "Availability of Companion Documents" field). In addition, they have added information for additional variant alleles not included in the original guideline (see Supplementary Tables S1 and S2 online).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. They have been adopted from the rating scale for evidence-based therapeutic recommendations on the use of retroviral agents (see the "Rating Scheme for the Strength of the Recommendations" field).

2013 Reaffirmation

The guideline authors reviewed recent literature and concluded that although relevant new evidence has been generated, none of the evidence would change the primary dosing recommendations in the original guideline; therefore, the original publication remains clinically current.

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

References Supporting the Recommendations

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Type of Evidence Supporting the Recommendations

The guideline authors have focused on presenting evidence from well-done studies and it is the interpretation of the results from these studies that provide the framework for the strength of the dosing recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

One of the benefits of preemptive thiopurine methyltransferase (*TPMT*) testing is that doses that are customized on the basis of TPMT status reduce the likelihood of acute myelosuppression without compromising disease control.

Potential Harms

- The risks of thiopurine methyltransferase (*TPMT*) testing would be that a proportion of heterozygotes may spend a period of time at lower thiopurine doses than they can eventually tolerate, because only ~30%–60% of heterozygous patients receiving conventional thiopurine doses experience severe myelosuppression. However, because steady state is reached in 2–4 weeks, any period of "underdosing" should be short, and in studies using this approach—at least in acute lymphoblastic leukemia and inflammatory bowel disease—outcomes were not compromised.

- A possible risk to the patient is an error in genotyping. Because genotypes are lifelong test results, any such error could stay in the medical record for the life of the patient.
- Some serious long-term adverse effects (secondary tumors) have been associated with the use of thiopurine therapy in patients with defective TPMT activity, even in the absence of severe acute myelosuppression; it is not known whether capping doses of thiopurines in those with a TPMT defect will ameliorate the risk of these late-developing adverse effects (secondary cancer). Some adverse reactions to thiopurines, such as pancreatitis and hepatotoxicity, are not related to low TPMT activity.

Qualifying Statements

Qualifying Statements

Qualifying Statements

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

Usually, thiopurines are administered orally every day for a period of at least several months. Genotype-based starting doses are just that—starting doses—and in most diseases, titration to an acceptable degree of myelosuppression is required. Clinicians should continue to evaluate markers of disease progression and/or myelosuppression to adjust thiopurine doses upward or downward from the genotype-directed starting doses. One caveat is that some serious long-term adverse effects (secondary tumors) have been associated with the use of thiopurine therapy in patients with defective thiopurine methyltransferase (TPMT) activity, even in the absence of severe acute myelosuppression; it is not known whether capping doses of thiopurines in those with a TPMT defect will ameliorate the risk of these late-developing adverse effects (secondary cancer). Some adverse reactions to thiopurines, such as pancreatitis and hepatotoxicity, are not related to low TPMT activity.

Disclaimer

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making, as well as to identify questions and settings for further research. New evidence may have emerged since the time a guideline was submitted for publication, which may or may not affect that guideline. The healthcare provider is responsible to check for updates to guidelines or subsequently published data. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the complete responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the informed and consenting patient. CPIC assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of CPIC's guidelines, or for any errors or omissions.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Relling MV, Gardner EE, Sandborn WJ, Schmiegelow K, Pui C-H, Yee SW, Stein CM, Carrillo M, Evans WE, Klein TE, Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. Clin Pharmacol Ther. 2011 Mar;89(3):387-91. [33 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Mar (reaffirmed 2013 Apr)

Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

Source(s) of Funding

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Guideline Committee

Not stated

Composition of Group That Authored the Guideline

2011 Guideline

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2013 Update

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Financial Disclosures/Conflicts of Interest

2011 Guideline

W.E.E. and M.V.R. have received patent royalties from TPMT genotyping tests. The other authors declared no conflict of interest.

2013 Update

M.V.R. and W.E.E. receive income from St. Jude for licensing patent rights for TPMT and GGH polymorphisms. They also receive funding for investigator-initiated research on the pharmacology of asparaginase from Sigma-Tau Pharmaceuticals.

Guideline Status

This is the current release of the guideline.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) reaffirmed the currency of the guideline in 2013.

Guideline Availability

Electronic copies: Available from the Pharmacogenomics Knowledgebase Web site .

Availability of Companion Documents

The following are available:

- Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. Clin Pharmacol Ther 2013 Apr;93(4):324-5. Electronic copies: Available in Portable Document Format (PDF) from the Pharmacogenomics Knowledgebase Web site .
- Supplementary material for the 2013 update, including tables and methodological information, is also available from the Pharmacogenomics Knowledgebase Web site .
- Supplementary material for the original guideline, including tables and methodological information, is available from the Pharmacogenomics Knowledgebase Web site .
- Interactive dosing tables are available from the Pharmacogenomics Knowledgebase Web site .

- "Look up" tables by gene, which contain phenotype and clinical support system information based on haplotypes and diplotypes, are available from the Pharmacogenomics Knowledgebase Web site .

Patient Resources

None available

NGC Status

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Copyright Statement

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